REMARKS

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, canceling claims 33-35, 38, 42-48, 50-59, and 137-142, and placing claims 119-132, 144-152, and 160-182 in condition for allowance. Applicants submit that the proposed amendments of claims 119-132, 144-152, and 160-173, and the addition of new claims 174-182 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

As discussed below, Applicants believe that entry of this Amendment will place the application in condition for allowance. In the pending final Office Action, the Examiner withdraws seven rejections of the claims as allegedly anticipated and/or obvious, leaving only rejections under 35 U.S.C. § 112 remaining.

On July 5, 2006, Examiners Woodward and Allen extended the courtesy of a telephonic interview to Applicants' representatives. In the interview, participants discussed the pending enablement and written description rejections, as well as the scope of the modified propeptides of the pending claims. The Applicants' representatives were given the opportunity to explain the nature of the invention, and to discuss enablement and written description of the percent identity, heterologous moiety, and fragment limitations of the pending claims with the Examiners. While the participants did not reach agreement in the telephonic interview, the Applicants thank the Examiners for focusing the issues remaining in this case. Additionally, Applicants

thank the Examiners for discussing the interpretation of dependent claims 147-152, and in particular, claims 151 and 152. Applicants sought the Examiners' clarification regarding how the enablement and written description rejections were applied to the subject matter of these claims. The Examiners explained that they interpreted claims 147-152 to encompass the fragments of part (a) (ii) of claim 144.

Based on the Examiners' guidance in the interview, Applicants file this Amendment to expedite allowance of this case. Applicants delete the "at least 75% identity" limitation throughout the claims, replacing it with "at least 95% identity." Applicants also delete claims to fragments of the amino acid sequences throughout, and delete "an optional heterologous moiety" from claim 144. Further, amendments to clarify and/or simplify the language of the claims have been made throughout, and Applicants cancel the withdrawn method claims at this time. Each of these changes is made in an earnest attempt to reach agreement on subject matter that would be allowable at this time. Applicants thus expressly reserve the option to pursue the cancelled subject matter in a subsequent application.

As discussed previously, this invention relates to the discovery that mutation of aspartate 76 in a GDF-8 propeptide sequence increases the half life and in vivo efficacy of the propeptide. The application describes mutations at this position in GDF-8 propeptides, referencing the many well-known GDF-8 sequences available to the skilled artisan, and it describes mutations at this position in BMP-11 propeptides, which are also disclosed with reference to the well-known BMP-11 sequences and available to the

skilled artisan at the time this application was filed.[1] *See, e.g.*, page 7, lines 4-12 and page 11, lines 3-11. The mutations of GDF-8 and BMP-11 propeptides are provided at page 18, line 16 to page 19, line 26. As would be apparent to one of ordinary skill in the art, residue 99 of SEQ ID NO:1 (which is residue 76 of SEQ ID NO:5) corresponds to residue 122 of SEQ ID NO:7 (which is residue 98 in SEQ ID NO:11). *See, e.g.*, Figure 14 and the explanation of the sequences provided previously in prosecution of this application. Similarly, the application states "exemplary amino acids mutatable to prevent cleavage of propeptide GDF-8 (amino acid numbers refer to SEQ ID NO:1) [include] . . . Asp-99." Thus, the application describes substitutions in GDF-8 and BMP-11 proteins of the application, which are described to encompass each well known family of proteins, see, e.g., page 7, lines 4-12 and page 11, lines 3-11.

Applicants note that the human GDF-8 and mouse GDF-8 propeptide sequences provided in the application are 94.7% identical when aligned using a FASTA algorithm (see Attachment B). An alignment of the human GDF-8 and BMP-11 propeptide sequences provided in the application shows that the BMP-11 propeptide sequence is approximately 50% identical to SEQ ID NO:5 (the human GDF-8 propeptide sequence

[1] In discussion of the presently claimed propeptides having a mutation at the residue corresponding to aspartate 76 of SEQ ID NO:5 (affecting internal cleavage of the propeptide by a protease), Examiner Allen suggested during the interview that a naturally occurring mutation in Belgium Blue or Piedmontesse cattle affects internal cleavage of the GDF-8 propeptide. As discussed in the interview, Applicants provide information regarding GDF-8 mutations in cattle with this response, which demonstrates that the cited mutations are not relevant to the novelty of the present claims. See Attachment A, Bellinge et al., *Animal Genetics* 36:1-6 (2004), which states at page 3, col. 1 that the Belgian Blue mutation is a premature termination in the mature GDF-8 protein, and Piedmontesse cattle have a substitution mutation in the mature GDF-8 protein, C313Y. Thus, neither mutation is in the GDF-8 propeptide and neither affects the in vivo or in vitro half life of the GDF-8 propeptide.

of the claims) (Attachment C). Both of the GDF-8 and BMP-11 propeptides reduce one or more of the biological activities of GDF-8. *See, e.g.*, page 16, lines 19-22.

Enablement

In the pending Office Action, the Examiner maintains the rejection under 35 U.S.C. § 112, alleging that the claimed genera of GDF-8 propeptides were too broad. The Examiner also suggests that Applicants have inaccurately characterized the modified GDF-8 propeptide in their March 6, 2006 response (*see* Office Action at page 5, lines 8-9). Applicants respectfully disagree, noting that Applicants' statement related to the scope of the claims, which further structurally and functionally characterized the modified GDF-8 propeptides. As the Examiner recognizes, the claims are to certain modifications that are provided and encompassed by the specification's support for the term "modified GDF-8 propeptides."

Applicants note that amended genera relate to sequences at least 95% identical to SEQ ID NO:5 (claims 119-132, 144-146, 160-170, 172-182), at least 96% identical (claim 147), at least 97% identical (claim 148), at least 98% identical (claim 149) at least 99% identical (claim 150), or identical to SEQ ID NO:5 (with an aspartate to alanine substitution at position 76 (claim 151), or with a mutation at position 76 (claim 152)). Claim 171 does not include a percent identity limitation, and has been amended to clarify the modification at the aspartate residue corresponding to Asp 76 of SEQ ID NO:5.

The amended claims also omit the fragments of parts (a)(ii) of claims 119, 144, 165 and 173, obviating that basis for the rejection of claims 119-132, 144-146, and 160-173. Applicants believe that pending claims 147-152 are directed to species of

GDF-8 propeptide that do not encompass the fragments of part (a) (ii) of claim 144, and thus that this basis for rejection does not apply to pending claims 147-152. Even if it were to apply, after amendment, this basis of rejecting the claims is moot.

Further, the amended claims omit the heterologous moiety of claim 144, rendering that basis for the rejection of claims 144-152 moot. While dependent claims 160-164 retain the claim term heterologous moiety, in each of these dependent claims the moiety is structurally characterized by a limitation in the dependent claim.

The specification discloses human and mouse GDF-8 propeptide species which are 94.7% identical, and it demonstrates their activity as inhibitors of GDF-8, for example in Figures 8 and 9. Thus, Applicants believe that the amended genera of claims 119, 144, 165, 171, and 173 (which incorporate a stabilizing mutation at a residue corresponding to asparate 76 of SEQ ID NO:5 to the well known propeptide genera) are well exemplified by the application as filed.

Applicants respectfully submit that the specification enables the full scope of polypeptides recited in the amended claims. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976). The Examiner has the initial burden of giving reasons, supported by the record as a whole, why the specification is not enabling. Id. The possibility that compounds satisfying a structural limitation may fail to fulfill a functional limitation does not establish lack of enablement. "Without undue experimentation or effort or expense the combinations which do not work will be readily discovered and, of course, nobody will use them and the claims do not cover them." Id. The skilled artisan need not be able to predict which structures will retain function; trial

and error experimentation is not necessarily undue. See, e.g., In re Wands, 858 F.2d 731 (Fed. Cir. 1988) (concluding that screening many hybridomas to find the few that fell within the claims was not undue experimentation).

In the instant case, the specification and knowledge in the art provide ample guidance as to changes that could likely be made to the sequence without disrupting activity. General guidelines for producing variants likely to retain activity were known in the art. Applicants' disclosure, combined with knowledge in the art, also provided guidance specific to the GDF-8 propeptides.

As argued previously, as discussed in the interview, and as summarized above, Applicants believe that the amended claims are enabled, and respectfully ask the Examiner to enter the amendment.

Adequate Written Description

The Examiner has rejected the claims as allegedly failing to meet the written description requirement of 35 U.S.C. 112, first paragraph. More specifically, the Examiner states that the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants amend the claims to expedite allowance, and to more clearly set forth the claimed subject matter. As detailed above, Applicants' support for the recited polypeptides exceeds the written description standard articulated by the PTO's own Guidelines. Example 14 of the Written Description Guidelines states that disclosure of a single protein sequence provides adequate written description support for the genus of proteins comprising sequences that are at least 95% identical to that sequence and

catalyze the reaction of A to B. As in Example 14, the instant claims relate to a polypeptide comprising an amino acid sequence that satisfies a functional limitation (inhibits a biological activity of GDF-8) and a structural limitation (at least 95% identical to SEQ ID NO:5, or in claims 147-152, at least 96%, 97%, 98%, 99%, or identical to the reference sequence (all with the proviso of containing a change at the residue corresponding to aspartate 76 of SEQ ID NO:5). As in Example 14, the specification and knowledge in the art provide procedures for making variants of the disclosed sequence and assays to identify variants satisfying the functional limitation, as the Examiner has recognized.

The skilled artisan could readily apply the information provided in the specification on the mouse and human GDF-8 propeptide sequences to designing the claimed polypeptides, as well as the information for the BMP-11 propeptide. An amino acid sequence that is at least 95% identical to SEQ ID NO:5 differs from the latter at no more than 12 amino acid positions. An alignment of the mouse and human GDF-8 propeptides (as well as eight other GDF-8 sequences) was well known in the art at the time of filing this application, and it is cited in the specification at page 7, lines 10-12. Based on conserved and divergent residues, the skilled artisan would recognize that the human sequence could likely be mutated to the corresponding amino acid of the mouse sequence at least at any of the divergent positions without disrupting activity.

The Examiner would seem to require that any claim reciting percent identity language be supported by experimental evidence showing which positions in the sequence can be changed without disrupting function. Such a requirement overstates the written description standard, which only requires that the skilled artisan recognize

that Applicants had possession of the claimed invention at the time of filing. Manual of Patent Examining Procedure § 2163, citing Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The skilled artisan would not require that functional variants be identified in the description; Example 14 shows that providing the reference sequence and methods to generate and test variants suffices to demonstrate possession. The instant specification exceeds that standard, in that the skilled artisan would also have the specific guidance provided by comparing mouse versus human GDF-8 propeptide and GDF-8 propeptide versus other TGF-β family members, as previously argued.

In short, Applicants' disclosure, considered in view of knowledge in the art, satisfies the written description standard articulated by the Federal Circuit in Vas-Cath, Inc. v. Mahurkar and by the PTO in the Written Description Guidelines. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

Furthermore, Applicants respectfully point out that the final action by the Examiner presented some new arguments as to the application of the art against Applicants' invention. It is respectfully submitted that the entering of the Amendment would allow the Applicants to reply to the final rejections and place the application in condition for allowance.

Finally, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is in conformance with the enablement and written description requirements of 35 U.S.C. § 112. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: August 10, 2006

By: /Mary K. Ferguson/
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Attachments A, B, and C